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EXAMINER
ELLIS, J

ART UNIT	PAPER NUMBER
1813	10

18N1/1018

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DATE MAILED: 10/18/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on 7/13/93 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~____~~ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 22 and 24-32 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-21 and 23 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 22 and 24-32 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Claims 22 and 24-32 are pending in the instant application with claims 1-21 and 23 cancelled by amendments filed in Paper Nos. 2, 3, and 9.

Due to the amendment submitted in Paper No. 9, all the claims are under consideration. Applicants title and abstract as amended in Paper No. 2 are no longer applicable to the claimed invention.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The IDS form is herein returned to applicants as requested. The references currently present in the predecessor applications have been duly acknowledged.

Claims 22 and 24-32 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,722,848 in view of Mackett et al., reference AX or Smith et al., reference BT. Mackett et al. and Smith et al. teach a method of producing proteins comprising transfecting eucaryotic cells with recombinant vaccinia viruses comprising a DNA sequence encoding heterologous proteins. Accordingly, it would have been obvious to one skilled in the art to employ the recombinant methods and recombinant vaccinia viruses claimed in U.S. Patent No. 4,722,848 to express the identical products in a culture of eucaryotic cells.

This is a *provisional* obviousness-type double patenting rejection.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as now claimed.

The specification as originally filed fails to teach a method for the production of (i) any protein, (ii) any enzyme, (iii) thymidine kinase, (iv) any glycoprotein, (v) herpes simplex virus glycoprotein, (vi) influenza virus hemagglutinin, (vii) any antigen, (viii) any herpes simplex virus glycoprotein antigen, (ix) any influenza virus antigen, or (x) the hepatitis B virus surface antigen, which comprises infecting a culture of eukaryotic cells with a recombinant vaccinia virus comprising a DNA encoding said proteins under suitable conditions to allow expression of the protein and isolating the expressed protein from the cell culture. Accordingly, the amendment to the claims constitutes the addition of new matter to the specification. Applicants must indicate the region(s) of the specification which supports the claims or cancel the new matter in response to the instant office action.

Claims 22 and 24-32 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by

the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure.

Assuming arguendo, that the specification does teach the claimed methods of producing proteins in cultures of eucaryotic host cells transfected with recombinant vaccinia viruses which comprise the DNA sequences encoding said proteins and isolating the expressed proteins from the cell culture, the specification fails to enable the subject matter of claims 22 and 24-31. It is well known in art that many factors affect the production of a heterologous protein in a eucaryotic cell. These include, inter alia, protein cytotoxicity, differences in post-translational modifications, changes in the three dimensional conformation, mRNA stability, the type of promoter, etc.. In view of the unpredictability of this art, the mere expression of three heterologous genes in cultures of eucaryotic cells is insufficient evidence to claim that all proteins, enzymes, glycoproteins, and antigens can be produced in eucaryotic cells transfected with a recombinant vaccinia virus which comprises the DNA sequence encoding these compounds. Further, the specification discloses that specific vaccinia virus constructs which comprise the DNA sequences encoding HSV TK (VP-2, VP-4, and VP-6), influenza virus hemagglutinin (VP 9), and the hepatitis B virus surface antigen (vP59) are capable of expressing their respective proteins in transfected eucaryotic cells. However, the nucleotide sequence of the heterologous DNA sequences which were employed is not disclosed. It is apparent that one skilled in the art cannot make and use VP-2, VP-4, VP-6, VP 9, or vP59 without knowing the

DNA sequence which was inserted into the recombinant vaccinia virus. As a required element, the precise nucleotide sequence employed in the construction of the recombinant vaccinia viruses must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 U.S.C. §112, first paragraph, have not been met. See MPEP §608.01(p)(C). It is noted that applicants have deposited the referenced recombinant vaccinia viruses; however, it is not clear whether all restrictions imposed by the depositor will be irrevocably removed upon the granting of a patent. That is, if a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. In the instant case both the deposit and the declaration must have been filed at the time of filing the parent applications in order for the disclosures to be enabling for the specific constructs taught therein.

Claims 22 and 24-32 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 22, and 24-31 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention.

Claim 22 is vague and indefinite in the recitation of a "protein". It is not clear what proteins applicants intend. The claim is also vague and indefinite in the recitation of "under suitable conditions to allow expression of the protein". It is not clear what culture conditions applicants intend. Finally, the claim is vague and incomplete in the recitation of "isolating the expressed protein from the cell culture". It is not clear what isolation procedures applicants intend.

Claim 24 is vague and indefinite in the recitation of an "enzyme". It is not clear what enzymes applicants intend.

In claim 25 it is not clear why "Kinase" has been capitalized.

Claim 26 is vague and indefinite in the recitation of a "glycoprotein". It is not clear what glycoproteins applicants intend.

Claims 27 and 30 are vague and indefinite in the recitation of a glycoprotein and antigen which is a "herpes simplex glycoprotein". It is not clear what glycoproteins and antigens applicants intend. Applicants are advised that when two claims in an application are duplicates or else so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to reject the other as being a substantial duplicate of the allowed claim. MPEP §706.03(k). Therefore, should the indicated claims be found allowable, the duplicate claim will be rejected under 35 USC §101.

Claims 28 and 31 are vague and indefinite in the recitation of a glycoprotein and an antigen which is an "influenza virus hemagglutinin". It is not clear what glycoproteins and

antigens applicants intend. Note comments with respect to claims 27 and 30, *supra*.

Claim 29 is vague and indefinite in the recitation of an "antigen". It is not clear which antigens applicants intend.

Claims 22, 29, and 32 are rejected under 35 U.S.C. § 103 as being unpatentable over Smith et al., reference BT, or Paoletti et al., reference BJ, in view of Sofer et al..

The important role of HBV as the etiological agent of both acute and late hepatitis in humans is well known in the art. Numerous laboratories have produced the highly immunogenic HBsAg to use as a human vaccine. Smith et al. and Paoletti et al. teach a method of producing HbSAg which comprises infecting a culture of eukaryotic cells with a recombinant vaccinia virus which comprises the DNA encoding HBsAg. For example, note Smith et al., Table 1. Sofer et al. broadly teach how to design optimal purification schemes using various purification techniques and Sofer et al. teach that HPLC methods have the ability to separate proteins which differ by as little as a single amino acid or that differ only in conformation. Accordingly, in view of the important pharmaceutical role of the HBsAg and the teachings of Smith et al. and Paoletti et al. as to a method of producing HBsAg by infecting a culture of eucaryotic cells with a recombinant vaccinia virus encoding the HBsAg, the teachings of Sofer et al. as to the standard methods in the art for protein isolation and purification and, absent an unexpected result, it would have been obvious to one of ordinary skill in the art to produce HBsAg using a recombinant vaccinia virus expression system and to further isolate said antigen to use in a vaccine formulation. It would have been obvious to employ known materials for their known

and expected results.

Claims 22, 24, and 25 are rejected under 35 U.S.C. § 103 as being unpatentable over Mackett et al., reference AX, in view of Sopher et al. and Bonnerjea et al..

Mackett et al. teach a method of producing thymidine kinase which comprises transfecting a culture of eucaryotic cells with a recombinant vaccinia virus which comprises the DNA sequence encoding thymidine kinase. Note Figure 4. Sofer et al. and Bonnerjea et al. broadly teach how to design optimal purification schemes using various purification techniques and Sofer et al. teach that HPLC methods have the ability to separate proteins which differ by as little as a single amino acid or that differ only in conformation. Given the teachings of Mackett et al. as to a method of producing thymidine kinase which comprises transfecting a culture of eucaryotic host cells with a recombinant vaccinia virus comprising the DNA sequence encoding thymidine kinase and the teachings of Sofer et al. and Bonnerjea et al. as to the standard methods in the art for isolating and purifying proteins and, absent an unexpected result, it would have been obvious to one of ordinary skill in the art to produce and isolate thymidine kinase using the methods and procedures taught by the references. It would have been obvious to employ known materials for their known and expected results.

Claims 22, 26, 27, and 30 are rejected under 35 U.S.C. § 103 as being unpatentable over Paoletti et al., reference BJ, in view of Bonnerjea et al. and Sofer et al..

Paoletti et al. teach a method of producing herpes simplex virus glycoprotein D which

comprises transfecting a eucaryotic cell with a recombinant vaccinia virus comprising a DNA sequence encoding said glycoprotein. Sofer et al. and Bonnerjea et al. broadly teach how to design optimal purification schemes using various purification techniques and Sofer et al. teach that HPLC methods have the ability to separate proteins which differ by as little as a single amino acid or that differ only in conformation. Given the teachings of Paoletti et al. as to a method of producing herpes simplex glycoprotein which comprises transfecting a culture of eucaryotic host cells with a recombinant vaccinia virus comprising the DNA sequence encoding herpes simplex glycoprotein and the teachings of Sofer et al. and Bonnerjea et al. as to the standard methods in the art for isolating and purifying proteins and, absent an unexpected result, it would have been obvious to one of ordinary skill in the art to produce and isolate herpes simplex glycoprotein using the procedures taught by the references. It would have been obvious to employ known materials for their known and expected results.

Claims 22, 26, 28, and 31 are rejected under 35 U.S.C. § 103 as being unpatentable over Smith et al., reference BS, in view of Sofer et al. and Bonnerjea et al..

Smith et al. teach a method of producing influenza virus hemagglutinin which comprises transfecting a eucaryotic cell with a recombinant vaccinia virus comprising a DNA sequence encoding said hemagglutinin. Sofer et al. and Bonnerjea et al. broadly teach how to design optimal purification schemes using various purification techniques and Sofer et al. teach that HPLC methods have the ability to separate proteins which differ by as little as a single amino acid or that differ only in conformation. Given the teachings of Smith et al. as to a method of

producing herpes simplex glycoprotein which comprises transfecting a culture of eucaryotic host cells with a recombinant vaccinia virus comprising the DNA sequence encoding herpes simplex glycoprotein and the teachings of Sofer et al. and Bonnerjea et al. as to the standard methods in the art for isolating and purifying proteins and, absent an unexpected result, it would have been obvious to one of ordinary skill in the art to produce and isolate influenza virus hemagglutinin using the procedures taught by the references. It would have been obvious to employ known materials for their known and expected results.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Ellis whose telephone number is (703) 308-3990.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Ellis, Ph.D.
October 13, 1993

JOAN ELLIS
PRIMARY EXAMINER
GROUP 180